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## Letter to the Editor

**Bradycardia due to remdesivir: Report of two cases<sup>\*</sup>*****Bradicardia por remdesivir: estudio de dos casos***

Dear Editor:

The current 2019 coronavirus disease (COVID-19) pandemic is posing a global scientific and health challenge in the generation of quality evidence. Very few treatments have proven to be effective, although several options have been proposed.<sup>1</sup> Remdesivir, a nucleotide analog with *in vitro* activity against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by inhibiting its ribonucleic acid (RNA) replication, is one of the most widely used and approved treatments for COVID-19 according to its summary of product characteristics. Because data obtained in clinical trials seem to indicate that hospitalized patients requiring low-flow oxygen therapy achieve the best results with this treatment, these are the types of patients in whom this drug's use is contemplated in the document prepared by the Spanish Health Ministry.<sup>2</sup> The aim of antiviral treatment with remdesivir is to prevent an increase in the severity of the disease, promote the patients' clinical recovery, and, thus, indirectly reduce the length of the hospital stay of COVID-19 patients. According to the drug's summary of product characteristics,<sup>3</sup> it is indicated for adults and teenagers with pneumonia secondary to a SARS-CoV-2 infection requiring supplemental oxygen therapy. The dose of remdesivir administered to patients  $\geq 12$  years and weighing at least 40 kg is 200 mg as a loading dose on the first day and 100 mg daily as of the second day, both administered through an intravenous infusion. The treatment's total duration should be at least 5 days and no more than 10 days. The most frequent adverse effects reported are transaminase level elevation, nausea, headache, and skin rash.<sup>3</sup>

In this paper we present two cases of symptomatic sinus bradycardia secondary to the administration of remdesivir in two patients with SARS-CoV-2 pneumonia.

The first patient is a 47-year-old overweight man with no pathological history who was admitted to the hospitalization ward due to presenting with bilateral pneumonia secondary to a SARS-CoV-2 infection. Because his oxygen saturation was 93%, oxygen therapy at a flow of 2 L/min was started, together with intravenous treatment with dexamethasone 6 mg/day, bemiparin 3500 IU/day, paracetamol 1 g/8 h, and inhaled drugs. Because he did not improve with this therapy, treatment with remdesivir was started while maintaining dexamethasone. After receiving the third dose of remdesivir, he developed symptomatic bradycardia with presyn-

cope symptoms, with sinus bradycardia (heart rate of 45 beats/min) being diagnosed. After discontinuing dexamethasone and remdesivir, treatment with intravenous boluses of methylprednisolone 250 mg/day was administered for three days owing to the potential heart involvement of the SARS-CoV-2 infection. Since he continued to exhibit signs of asymptomatic bradycardia (heart rate of 49–50 beats/min), a Holter monitor study was carried out, detecting sinus rhythm readings. The bradycardia gradually resolved within the 72 h following the drug's withdrawal. He was eventually discharged nine days after his initial admission with an improved and stable condition.

The second patient is a 74-year-old hypertensive man who was diagnosed with a non-operable squamous cell lung cancer in May 2020 and treated with chemoradiotherapy with curative intent. On admission, the patient presented with respiratory failure secondary to moderate pneumonia caused by a SARS-CoV-2 infection, owing to which treatment with ceftriaxone 2 g/day, azithromycin 500 mg/day, bemiparin 5000 IU/day, as well as chronic ambulatory medication (losartan 50 mg/day and tamsulosin 0.4 mg/day) was started. As he did not improve, three boluses of intravenous methylprednisolone 125 mg/day and remdesivir at the standard dose were added to his treatment regimen. After receiving the third dose of remdesivir, he developed sinus bradycardia (heart rate of 45 beats/min), owing to which remdesivir and azithromycin were discontinued. The bradycardia resolved within the following 24 h and, once his clinical condition had improved, he was discharged from the hospital two days later.

We conducted a search in PubMed using terms "adverse drug reaction" and "remdesivir", identifying hypotension secondary to the drug's infusion as a potential adverse reaction described in the available literature,<sup>4</sup> in addition to atrial fibrillation.<sup>5</sup> However, no cases of bradycardia similar to those reported in this paper have been reported to date. Remdesivir is a drug with few data available on its use and for which the mechanism of action and safety profile have not yet been described in detail.

After applying the modified Karch and Lasagna causality algorithm used by the Spanish Pharmacovigilance System for Medicines for Human Use (SEFV-H, Sistema Español de Farmacovigilancia de Medicamentos de Uso Humano), both adverse drug reactions (ADRs) were classified as possible (4 points) and reported through a yellow card notice to the SEFV-H.

The pharmacist's role is crucial in ensuring patient safety, and the notification of adverse effects is a key aspect of pharmacovigilance, particularly when using therapies for which there is limited experience in terms of their management.

Knowing both the efficacy and safety profile of the therapies used in the treatment of COVID-19 is an additional challenge for healthcare professionals in relation to which we must always maintain a critical and cautious attitude owing to the avalanche of information to which we are being subjected.

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